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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,796	09/03/2003	Nicholas P. Barker	50206/013003	5419

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,796	BARKER ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-29* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-21, drawn to a modified asialo-interferon, classified in class 424, subclass 85.4.

II. Claims 22-29, drawn to a method of treating a patient with a hepatic disorder by administration of an asialo-interferon, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the modified asialo-interferon can be used in materially different process, such as in the treatment of multiple sclerosis.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are

governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Paul Clark on 2/21/2006, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-21. Affirmation of this election must be made by applicant in replying to this Office action. Claims 22-29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement filed on 6/29/2004 has been fully considered by the Examiner.

Specification

The use of the trademarks Wellferon, Alferon, Multiferon, and Infergen (p. 4, lines 13-19) has been noted in this application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term "asialo-interferon" are not clear. The specification, on page 5, lines 24-25, defines an asialo-interferon as "a glycosylated interferon lacking a terminal sialic group that is present in the native glycoslylated interferon." Pages 18-20 of the specification describe methods of producing asialo-interferons, including recombinant methods, and on page 19, lines 21-24, states that the precise host cell used to produce interferons is not critical to the invention. It is known in the art, however, that not all host cells sialylate recombinant proteins. For example, some insect and plant cells are known to produce non-sialylated recombinant proteins (Marchal *et al*, 2001, Biol. Chem., Vol. 382, pages 151-159; Altmann *et al*, 1999, Glycoconjugate J., Vol 16, pages 109-123; Sugyiami *et al*, 1993, Eur. J. Biochem., Vol 217, pages 921-927; Goochee *et al*, 1991, Bio/Technology, Vol. 9, pages 1347-1355). Additionally, the yeast *Saccharomyces cerevisiae* lacks the enzymes β1,4 galactosyltransferase and α2,6 sialyltransferase, and glycans from *S. cerevisiae* lack galactose and sialic acid residues (Krezdorn *et al*, 1994, Eur. J. Biochem., Vol. 220, p. 809-817). Thus, asialo-interferons can be produced by methods disclosed in the specification, or via recombinant methods in a host cell incapable of sialylation. Furthermore, given the broadest reasonable interpretation, the claims, which do not define or limit the type or source of the claimed asialo-interferon(s), read on any interferon lacking a terminal sialic acid residue. For

the purposes of examination, the examiner has interpreted "asialo-interferon" as any interferon, from any source, that lacks a terminal sialic acid residue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7, 11-12, 15-19, and 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by DeFrees *et al* (US 2004/0082026, which is supported by *at least* provisional application 60/407,527, and therefore has a priority date of *at least* 8/28/2002). The claims of the instant application are drawn to a modified asialo-IFN conjugated to a water-soluble polymer. The claims are further drawn to asialo-IFN conjugated to PEG, and pharmaceutical compositions thereof. DeFrees *et al* teaches pegylation of asialo-IFN molecules, including IFN-α and β (see paragraphs 1683 – 1701). Specifically, PEG of 10 kDa and 20 kDa is taught (paragraph 1689). Thus, DeFrees anticipates the limitations of claims 1-3 of the instant application. DeFrees also teaches modification of human IFN α, β, and γ polypeptides (paragraph 1188), and therefore meets the limitations of claims 11-12 of the instant application. Finally, DeFrees teaches pharmaceutical compositions of the modified IFN polypeptides (paragraph 0117). Taken together, the teachings of DeFrees meet the limitations of claims 15-18 and 20-21 of the instant application, which are drawn to pharmaceutical compositions of pegylated human asialo-IFN molecules.

In additional, the claims of the instant application are drawn to asialo-IFN polypeptides that are pvpylated. DeFrees *et al* also teaches the use of polyvinylpyrrolidone (PVP) as a water-soluble polymer that can be used to modify IFN polypeptides (parapgraph 0734), and pharmaceutical compositions of modified IFN polypeptides (see above), thus meeting the limitations of claims 7 and 19 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeFrees *et al* in view of Monkarsh *et al* (Anal. Biochem, 1997, Vol. 247, pages 434-440), and further in view of Shadle *et al* (US 4,847,325). The claims are drawn to pegylation of an asialo-IFN, wherein the asialo-IFN is pegylated on specific amino acid residues, including cysteine or lysine. As discussed above, DeFrees *et al* teaches pegylation of asialo-IFN; however, it is silent regarding pegylation of any specific amino acid residue. Monkarsh et al teaches a method of pegylation of IFN-α2a involving urea linkage of PEG to N-terminal amino groups or lysine residues (page 434, 3rd paragraph). Using this method, Monkarsh *et al* show that all 11 lysine residues of IFN-α2a can be pegylated (see p. 437-438 and Tables I and II). Shadle *et al* teaches pegylation of polypetides, including interferon-beta, on cysteine residues (column 3, lines 16-18; column 4, lines 45-55).

A person of ordinary skill in the art would be motivated to practice the invention of claims 4-6 by combining the teachings of DeFrees *et al*, which teaches pegylation of asialo-IFN, with the teachings of Monkarsh *et al*, which teaches pegylation of lysine residues, and the teachings of Shadle *et al*, which teaches pegylation of cysteine residues. DeFrees *et al* demonstrates methods for producing asialo-IFNs and also teaches pegylation of these asialo-IFNs, while Monkarsh *et al* and Shadle *et al* teach specific methods for pegylation of specific amino acid residues. Thus, the skilled artisan would have both the motiavation, but also a reasonable expectation of success, in practicing the instant invention by combining the teachings of DeFrees *et al*, Monkash *et al*, and Shadle *et al*.

2. Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeFrees *et al* in view of Shadle *et al* (US 4,847,325). The claims are drawn to asialo-IFNs comprising additional cysteine residues compared to the mature polypeptide sequence. DeFrees *et al* teaches methods for preparing asialo-IFNs, but does not teach introduction of any

additional cysteine residues into the asialo-IFN polypeptide sequences. Shadle *et al* teaches pegylation of cysteine residues (see above), and also teaches introduction of additional cysteine residues into a polypeptide sequence (column 9, lines 14-18; column 12, lines 17-21). A skilled artisan would be motivated to following the teachings of DeFrees *et al* and Shadle *et al* to produce asialo-IFN with additional cysteine residues, including replacing threonine or serine with cysteine. Because DeFrees *et al* teach methods for preparing asialo-IFNs, and Shadle *et al* teaches introduction of additional cysteine residues into a polypeptide sequence, one of ordinary skill in the art would also have a reasonable expectation of success in producing asialo-IFN polypeptides comprised of additional cysteine residues.

3. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* (1983, Molec. Cell. Biol., Vol 3, No. 12, p. 2156-2165), in view of Monkarsh *et al*, and further in view of Shadle *et al*, and further in view of Francis (1992, Focus on Growth Factors, Vol. 3, p. 4-10). The claims of the instant invention are discussed above. Smith *et al* teaches production of human IFN-β in insect cells. It is known in the art that recombinant proteins produced by insect cells are not sialyated (see Marchal *et al*, Altmann *et al*, Sugyiami *et al*); thus, Smith et al teaches an asialo-IFN-β polypeptide. Smith et al does not teach pegylation of this asialo-IFN-β polypeptide. The teachings of Monkarsh *et al* and Shadle *et al* are discussed above. Francis teaches that polyvinylpyrrolidone (PVP) is a common chemical modifier of proteins and polypeptides.

One of ordinary skill in the art would be motivated to combine the teachings of Smith *et al* with those of Monkarsh *et al*, Shadle *et al*, and Francis to practice the claimed invention. Smith et al provides the skilled artisan with a method of producing an asialo-IFN, and Monkarsh *et al* and Shadle *et al* provides the skilled artisan the motivation to modify the asialo-IFN via pegylation, while Francis provides the motivation to modify the asialo-IFN via pvpylation. Furthermore, Monkarsh *et al* and Shadle *et al* provide the motivation for modification on lysine or cystiene residues, respectively, and Shadle *et al* also provides the motivation for the incorporation of additional cysteine residues. Finally, Smith et al, by teaching that IFN-b has antiviral, antiproliferative, and antitumor properties, would provide the skilled artisan the motivation to incorporate the modified asialo-IFN in a pharmaceutical composition. Therefore, one of ordinary skill in the art would not only have the motivation to combine the teachings of Smith *et al* with those of Monkarsh *et al*, Shadle *et al*, and Francis, to practice the claimed

invention, but also a reasonable expectation of success in producing the claimed modified asialo-IFN.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BDH
Art Unit 1646

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